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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,142	KYRKANIDES, STEPHANOS	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-143* is/are pending in the application.

4a) Of the above claim(s) *44-71,76-82 and 92-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43,72-75,83-91 and 133-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Action of October 4, 2006 on April 4, 2007. No amendments to the claims have been filed. As such, Applicant's response will be considered in view of the claims filed July 27, 2006.

Claims 44-71, 76-82, 92-132 are withdrawn. This application contains claims 44-71, 76-82, 92-132, drawn to an invention nonelected with traverse in the reply filed on October 21, 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-43, 72-75, 83-91, and 133-143 are under consideration.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-43, 72-75, 83-91, and 133-143 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) a nucleic acid construct comprising a promoter operably linked to a nucleotide sequence comprising two cistrons and a nucleotide sequence that provides IRES activity operably linked to the cistron subsequent to the first cistron, wherein the first cistron encodes HEX-beta, wherein the sequence is set forth in SEQ ID NO. 3, and wherein the second cistron encodes HEX-alpha, wherein the sequence is set forth in SEQ ID NO. 1.

2) a nucleic acid construct comprising a promoter operably linked to a nucleotide sequence comprising two cistrons and a nucleotide sequence that provides IRES activity operably linked to the cistron subsequent to the first cistron, wherein the first cistron encodes HEX-alpha, wherein the sequence is set forth in SEQ ID NO. 1, and wherein the second cistron encodes HEX-beta, wherein the sequence is set forth in SEQ ID NO. 3.

3) a composition comprising a nucleic acid construct comprising a promoter operably linked to a nucleotide sequence comprising two cistrons and a nucleotide sequence that provides IRES activity operably linked to the cistron subsequent to the first cistron, wherein the first cistron encodes HEX-beta, wherein the sequence is set forth in SEQ ID NO. 3, and wherein the second cistron encodes HEX-alpha, wherein the sequence is set forth in SEQ ID NO. 1.

4) a composition comprising a nucleic acid construct comprising a promoter operably linked to a nucleotide sequence comprising two cistrons and a nucleotide sequence that provides IRES activity operably linked to the cistron subsequent to the first cistron, wherein the first cistron encodes HEX-alpha, wherein the sequence is set forth in SEQ ID NO. 1, and wherein the second cistron encodes HEX-beta, wherein the sequence is set forth in SEQ ID NO. 3.

does not reasonably provide enablement for

any nucleic acid construct or composition comprising a nucleic acid construct comprising a promoter operably linked to a nucleotide sequence comprising two cistrons and a nucleotide sequence that provides IRES activity operably linked to the cistron subsequent to the first cistron, wherein the first cistron encodes any HEX-alpha, other than SEQ ID NO. 1, and wherein the second cistron encodes any HEX-beta, other than SEQ ID NO. 3.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record, June 6, 2005, January 27, 2006, and October 4, 2006.

Applicant's arguments filed April 4, 2007 have been fully considered and they are persuasive in part.

Applicant indicates that the claims have been amended to separately recite 95%, 85%, and 70% sequence identities and added functional limitation to claims 1 and 72, i.e., the ability to catabolize GM_2 ganglioside. Applicant indicates that the Examiner has apparently interpreted this amendment to cover any mutant, stating, "screening without guidance as to what structure of HEXA and HEXB would need to be conserved to arrive at a functional protein is not enabled (Applicant's emphasis, Applicant's response, page 2-3). To clarify this issue, Applicant is claiming a genus of molecules based on structure and function and that the structure of HEX-alpha and HEX-beta were known and described in the specification (Applicant's response, page 3). In response, the issue that Applicant discusses relates to Written Description and the Examiner will discuss this issue in the Written Description rejection, see below.

Applicant indicates that the present rejection depends only on the question of whether, in view of the specification and knowledge of those of skill in the art at the time the invention was made (as evidenced by the complete record in this application), the compositions recited in claims 1-43, 72-75, 83-91, 133-143 could be made and used by those of skill in the art without the need for undue experimentation (Applicant's response, pages 3-4). Applicant indicates that the predictability for the function of a protein having at least 70% sequence identity to a known protein is greater than 90%. This assumes that no specific information regarding conserved

regions of the protein are known (i.e. random mutations). However, specific mutations in HEX-alpha and HEX-beta that cause neurological disorders were known in the art (Gravel, et al., 1991, Neufeld, 1989). Thus, the skilled artisan would know to at least avoid these specific mutations, making the predictability even higher (Applicant's emphasis, Applicant's response, page 6, 1st parag. under "b) Predictability of Function based on Sequence Identity"). With regard to specific mutations in HEX-alpha and HEX-beta (e.g. Gravel et al., 1991), Gravel et al. teach 9 amino acid substitutions and one amino acid deletion in HEX-alpha (Gravel et al., Table 1). This does not provide support for the wide variety of single (and multiple) amino acid substitutions, deletions, and additions for each position in the HEXA protein sequence. With regard to Applicant referring to Neufeld, Neufeld indicates that the beta-subunit has not been studied in the same detail as the alpha-subunit mutations (Neufeld, page 10929, 2nd col. under "β-Subunit Mutations". Neufeld does not provide any guidance of any amino acids or regions within the beta-subunit (HEXB), such that an artisan can arrive at the genus of amino acid sequences of the beta-subunit that catabolize GM_2 ganglioside. As such, because there is no guidance in selecting particular regions and domains which can be mutated with amino acid substitutions, deletions, and additions, an artisan is reduced to trial and error (and hence, the Examiner alluded to identifying the claimed proteins with a particular biological activity via a screen), in order to arrive at the genus of HEXA and HEXB proteins that have activity. It is noted that the invention is not limited to single amino acid changes, deletions, and additions; the invention also encompasses proteins with multiple mutations as well. Without any guidance of what region(s) within HEXA and HEXB should be avoided, in order to arrive at a functional protein, an artisan would resort to trial and error, in order to find functional proteins.

Applicant indicates that a case has been made to support the predictability for sequences for variants of at least 70% identity. Applicant indicates that the Examiner has misinterpreted the Applicant's summary of the findings of Tian and Skolnick, 2003 used to support this position. Applicant indicates that in response, the Examiner stated that while most protein mutants may maintain enzyme function, the assertion does not indicate to an artisan how to discriminate the 10% of the mutants which do not have activity (Applicant's emphasis, Applicant's response, page 7). Applicant indicates that 90% predictability combined with the skill of the artisan for assaying GM_2 ganglioside catabolysis would not constitute undue experimentation. Applicant indicates that there is no evidence either in Tian and Skolnick or in the art that any mutations within this range, other than the ones already known in the art to cause disease would in fact result in a non-functional mutant. In response, this is not persuasive. According to Tian and Skolnick, functional divergence can happen at high levels of sequence identity, where there is no dispute about homology (Tian and Skolnick, page 872, 2nd col., 1st parag. under "How well is enzyme function conserved?"). Because neither the art nor the specification provide any guidance that functional divergence does not occur at high levels of sequence identity with HEXA and HEXB, an artisan cannot reasonably predict that Applicant's assertion that any mutations in HEXA and HEXB other than the ones already known would not result in a non-functional mutant. Conversely, it is noted that the claims encompass proteins which catabolize GM_2 ganglioside and encode a protein other than HEXA and HEXB, including those not yet known in the art. Note for example that Tian and Skolnick, Table A1, page 880, teach two distinct rabbit proteins, LOX2 and LOX1, which have 99% identity, yet encode different proteins. The specification does not provide guidance for discriminating HEXA and

HEXB from proteins that are similar in sequence to them and yet encode different proteins. It is also noted that the claims encompass compositions wherein function is not recited (e.g. claims 84, 85) and the specification does not provide guidance on arriving at various HEX-beta or HEX-alpha sequences based on name. Because there is no guidance in obtaining HEXA and HEXB that have 70-95% identity to SEQ ID NOs. 1 and 3, an artisan is not enabled to practice the claimed invention.

With regard to claim 1 is drawn to a composition comprising an isolated nucleic acid sequence wherein the nucleic acid comprises a sequence encoding HEX-alpha and a sequence encoding a HEX-beta, Applicant does not agree that a promoter driving expression of the nucleic acids encoding HEX proteins is necessary to enable the composition. Applicant indicates that gene constructs are routinely provided as cassettes for transfer to selected expression vectors (Applicant's response, page 8). In response, the Examiner finds Applicant's response persuasive and withdraws the rejection as it applies to this issue.

Claims 1-43 72-75, 83-91, and 133-141 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record, June 9, 2005, January 27, 2006, and October 4, 2006.

Applicant's arguments filed April 4, 2007 have been fully considered but they are not persuasive.

Applicant indicates that the instant claims do not attempt to define the composition with only a wish or plan. This would only be vaild if the claim were to a composition comprising a nucleic acid encoding any protein that catabolize GM_2 ganglioside, i.e., with no structural limitation. Such claim would be attempting to describe the composition entirely by function and/or a means of identifying compositions having that function. In contrast, the present claims are limited to nucleic acids encoding HEX-alpha and HEX-beta, which have a defined structure (Applicant's response, page 9, 2nd parag.). In response, this is not persuasive. The claims encompass a genus of nucleic acid sequences that encode HEXA and HEXB, wherein the encoded proteins have 70-95% sequence identity to those of SEQ ID NOs. 1 and 3. While the specification teaches SEQ ID NOs. 1 and 3, the specification does not provide structural/functional guidance such that an artisan could arrive at the genus of HEXA and HEXB proteins having 70-95% sequence identity and having the activity of catabolizing GM_2 gangliosides. Rather, to arrive at 70-95% identical sequences that have the activity of catabolizing GM_2 gangliosides, an artisan would be reduced screening proteins that are 70-95% identical to proteins of SEQ ID NOs. 1 and 3, in order to find those that fit the claims criteria.

Applicant indicates that the USPTO has established that variants can be claimed based on sequence identity (Example 14 of USPTO "Synopsis of Application of Written Description Guidelines"), wherein the single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay (Applicant's response, page 9, 2nd parag.). In response, this is not persuasive. It should be noted that the interim guidelines published December 21, 1999 are only guidelines and emphasize that compliance with the written description requirement will be

determined by a case by case basis; and that the examples provided therein are not designed to be applied on an absolute basis, as additional factors relating to a particular paradigm also need to be considered.

The claims encompass nucleic acid molecules that encode variant sequences having at least 95% sequence identity to the proteins of SEQ ID NOs. 1 and 3, and numerous nucleic acid molecules that encode SEQ ID NOs. 1 and 3, which retain the biological activity of HEXA and HEXB, and are yet to be discovered. The specification merely discloses cDNA nucleotide sequences encoding human HEXA and HEXB (SEQ ID NOs. 2 and 4). Applicant's specification provides no description of nucleotide sequences variants that encode SEQ ID NOs. 1 and 3 that retain the biological activity of HEXA and HEXB protein, or any nucleic acid molecules obtained using any polynucleotide that encode SEQ ID NOs. 1 and 3, that retain the biological activity of HEXA and HEXB protein. Hence, only the nucleotide sequence that of the full length human HEXA and HEXB nucleic acids as set forth in SEQ ID NOs. 2 and 4 and a nucleotide sequence that encodes proteins having the amino acid sequence of SEQ ID NOs. 1 and 3 could be demonstrated as possessed.

As previously indicated, to satisfy the written description requirement, Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. As stated in MPEP 2163, "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). The issue is not whether

protocols for making polynucleotides variants were known in the art at the time of Applicants' filing. The function of the written description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied on, the specific subject matter later claimed by him or her; how the specification accomplishes this is not material. *In re Herschler*, 591 F.2d 693, 700-01, 200 USPQ 711, 717 (CCPA 1979) and further reiterated in *In re Kaslow*, 707 F.2d 1366, 707 F.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983).

Applicants have failed to disclose sufficient core structure and function related to that core structure such that a person of skill could determine HEXA and HEXB biological activity by being directed to sequences encoding said core structure. With regard to HEXA and HEXB biological activity, Applicant's specification only discloses that the proteins form a complex and catabolize GM2 (specification, page 14, 2nd parag. under "Tay-Sachs & Sandhoffs disorders"); however, no guidance was provided with regard to the structure(s) that contribute to this activity. As stated in MPEP 2163 II: if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. In contrast, without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. In this latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

Applicant indicates that the Applicant is claiming a genus of molecules based on structure and function (Applicant's response, page 3, 3rd parag.). Applicant indicates that the structure of HEX-alpha and HEX-beta were known and described in the specification. Further, the claims stand rejected (claim 138) that restrict the structure of HEX-alpha and HEX-beta to a sequence identity of as high as 95% to the known structure. The Examiner has characterized this as "screening for mutants that fit the functional criteria" and stated that this does not enable an artisan to arrive at the claimed invention. Applicant indicates that the claim is not a product-by-process resulting from a screening method. Rather, a genus of molecules is provided based on the known structure of HEX-alpha and HEX-beta, and a function, i.e., the ability to catabolize GM_2 ganglioside. Applicant indicates that this does not constitute a screening process because the genus of compounds is defined by structure, here, the sequence for HEX-beta is SEQ ID NO.3 and the sequence for SEQ ID NO. 1 is HEX-alpha, which defines the structure of these proteins and nucleic acids that encode them. Thus, a genus of compositions is therefore provided based on the variance of these structures (Applicant's response, page 3, 3rd parag.). In response, this is not persuasive. While the proteins of SEQ ID NOs. 1 and 3 are understood to have the activity of catabolizing GM_2 gangliosides, this does not provide guidance for an artisan to arrive at the genus of protein sequences that are 70-95% identical to SEQ ID NOs. 1 and 3, wherein the proteins have the activity of catabolizing GM_2 gangliosides. This is because the claims encompass a wide variety of single and multiple amino acid substitutions, deletions, and additions, wherein single and multiple amino acid substitutions, deletions, and additions can lead to changes in tertiary enzyme structure and thus affect function (e.g. dominant negative mutations). While Applicant relies on Tian and Skolnick for enabling the claimed nucleic acids

and providing written description for sequences 70%-95% identical to SEQ ID NOs. 1 and 3, Tian and Skolnick provide guidance following classification of enzyme families (oxidoreductases, transferases, hydrolases, lysases, isomerases, and ligases; Tian and Skolnick, page 864, 1st col., 3rd parag.), wherein the domains and enzymatic functions of the proteins that comprise them are well-characterized. Tian and Skolnick do not provide guidance that a particular kind of enzyme, one that catabolizes GM_2 gangliosides, necessarily would have activity similar to that of the wild type protein if 70-95% of HEXA or HEXB were mutated. It is noted that Tian and Skolnick cannot be read to indicate that less than 70% sequence identity of a protein is a point at which enzyme function starts to diverge is readily applicable to all types of proteins as Tian and Skolnick teach that functional divergence can happen at high levels of sequence identity, where there is no dispute about homology (Tian and Skolnick, page 872, 2nd col., 1st parag. under "How well is enzyme function conserved?"). Thus, while Tian and Skolnick provide general insight about the groups of proteins they studied, their studies do not provide written description for the 70-95% sequence identities of particular proteins, such as HEXA and HEXB, as claimed.

Thus, the claims remain rejected.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of

document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Joanne Hama
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/Anne Marie S. Wehbé/
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